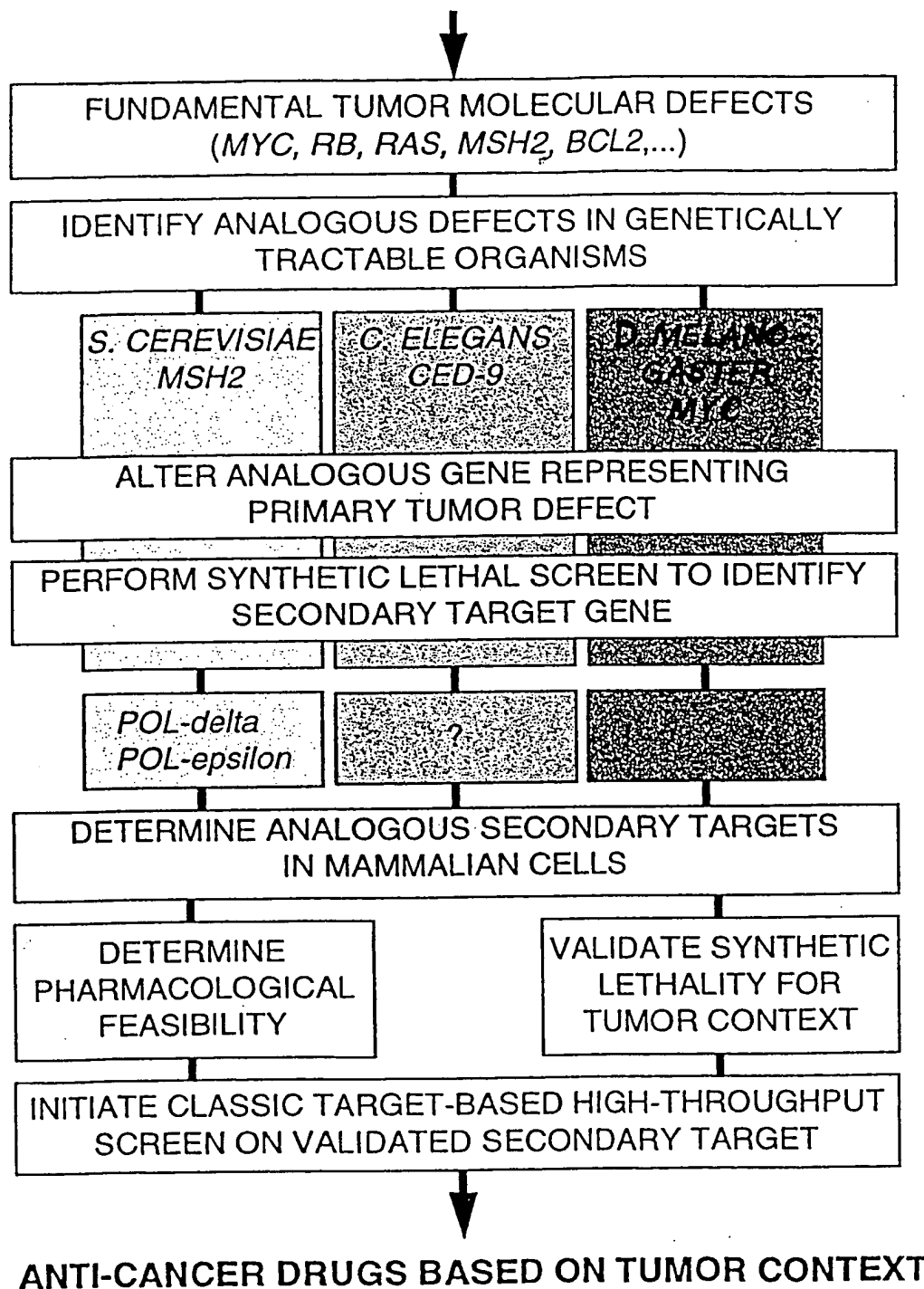
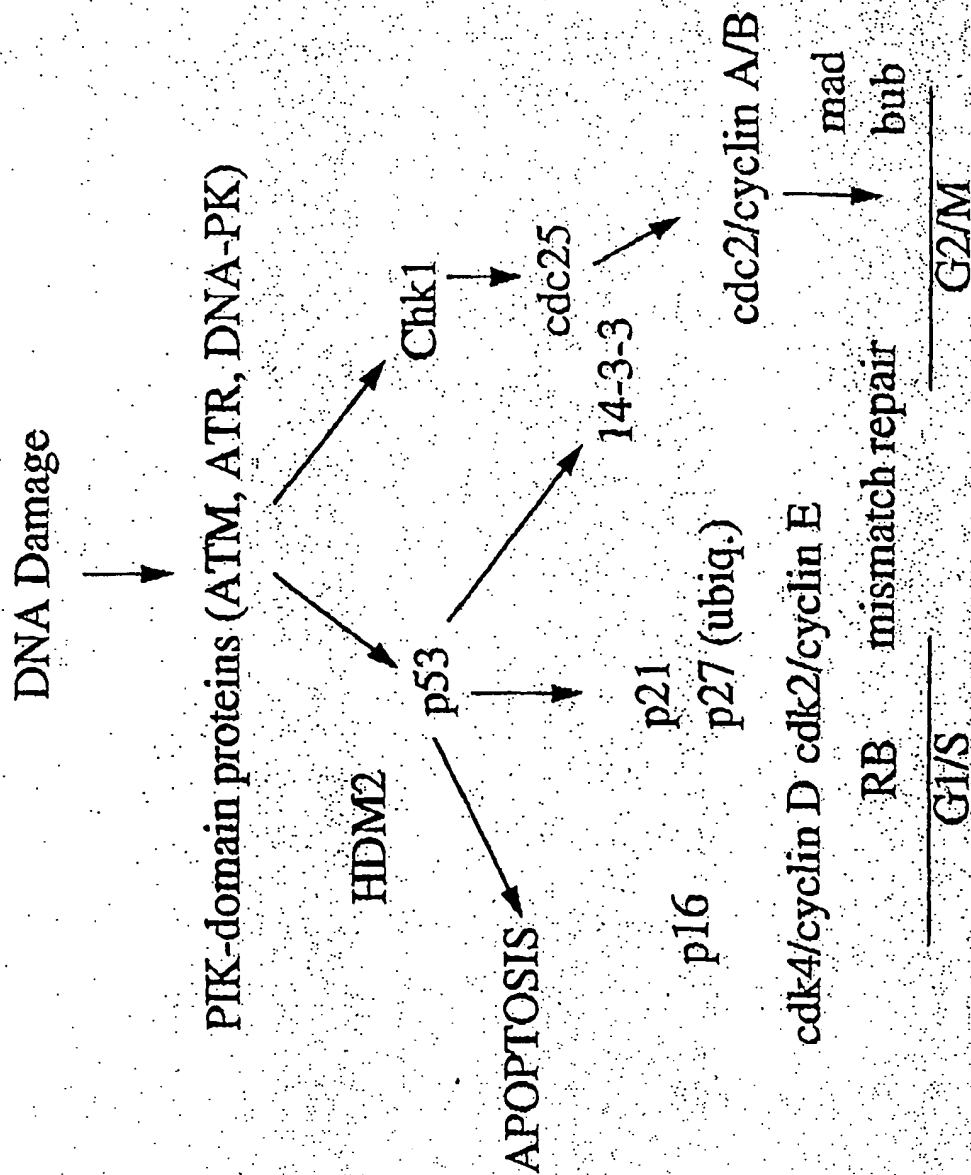


FIGURE 1

MOLECULAR ALTERATIONS IN TUMORS



Cell Cycle/DNA Damage Response Pathways

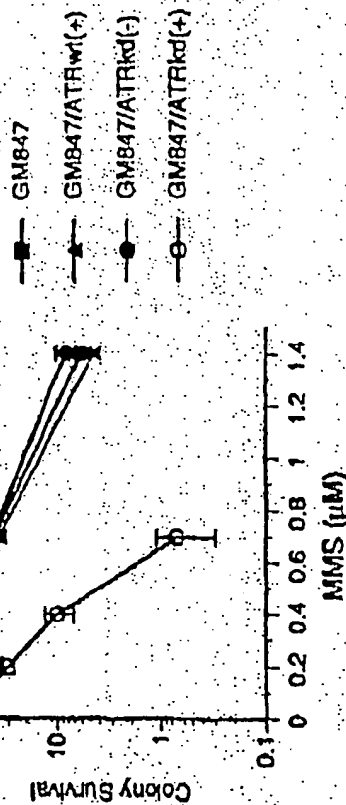


MAMMALIAN CELL EVALUATION OF ATR AS A TARGET

1. Overexpression of ATR-KD not tolerated in human tumor cell lines (MCF-7, A549)

2. Inducible ATR-KD sensitizes cells to DNA damaging agents

Figure 3



3. LCK promoter driven ATR-KD transgenic mice have cells stably expressing ATR-KD in thymus

Figure 4

Synthetic lethality:

- Use primary defect as a selective context to kill tumor cells with an alteration in gene A.
- Combined defects in gene A and gene B kill tumor cells while disrupting gene B activity alone has no effect on normal cells.

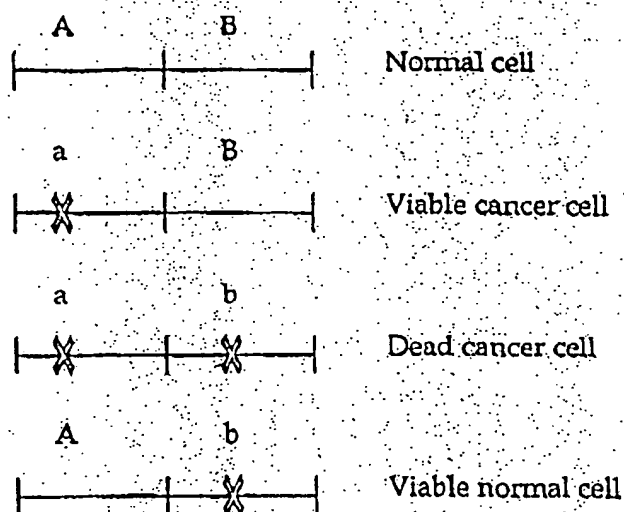


Figure 5

Human genes altered in tumors and their relatives in model genetic systems. Genes that are not structural homologs but act in analogous pathways (such as human p53 and *S. cerevisiae* RAD9) are shown in brackets. *Saccharomyces cerevisiae* genes are designated with superscript Sc, *S. pombe* with Sp, *C. elegans* with Ce, and *D. melanogaster* with Dm. Because of space limitations, this is only a representative list of genes mutated in tumors that have genetic analogs in model systems.

Function	Human genes	Model system analogs: structural homologs or related biological roles
DNA damage checkpoint	p53	[RAD9 ^{Sc} , rad1 ^{-Sp}]
	ATM	MEC1 ^{Sc} , TEL1 ^{Sc} , rad3 ^{3+Sp} , mei-41 ^{Dm}
DNA mismatch repair	MSH2, MLH1	MSH2 ^{Sc} , MLH1 ^{Sc}
Nucleotide excision repair	XP-A, XP-B	RAD14 ^{Sc} , RAD25 ^{Sc}
O ⁶ -methylguanine reversal	MGMT	MGT1 ^{Sc}
Double-strand break repair	BRCA2, BRCA1	[RAD51 ^{Sc} , RAD54 ^{Sc}]
DNA helicase	BLM	SGS1 ^{Sc} , rqh1 ^{-Sp}
Growth factor signaling	RAS	RAS1 ^{Sc} , RAS2 ^{Sc} , let-60 ^{Ce}
	NF1	IRA1 ^{Sc} , IRA2 ^{Sc}
	MYC	dMyc ^{Dm}
	PTH	patched ^{Dm}
Cell cycle control	Cyclin D, Cyclin E	CLN1 ^{Sc} , CLN2 ^{Sc} , Cyclin D ^{Rm} , Cyclin E ^{Dm}
	P27 ^{rod1}	[SIC1 ^{Sc}]
	Rb	Rbf ^{Dm}
Apoptosis	BCL-2	ced-9 ^{Ce}

Cell Cycle/DNA Damage Response Pathways

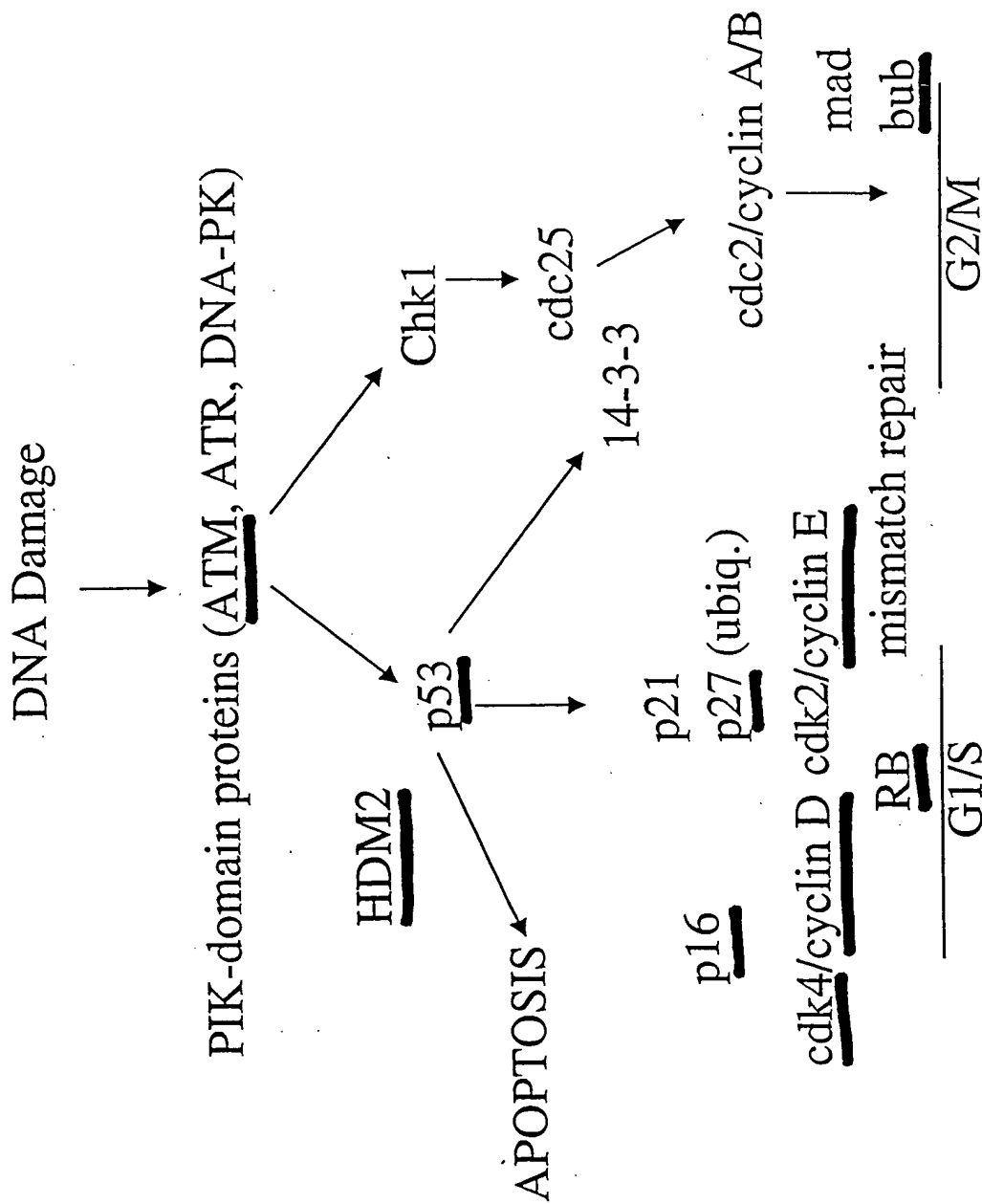


Figure 6

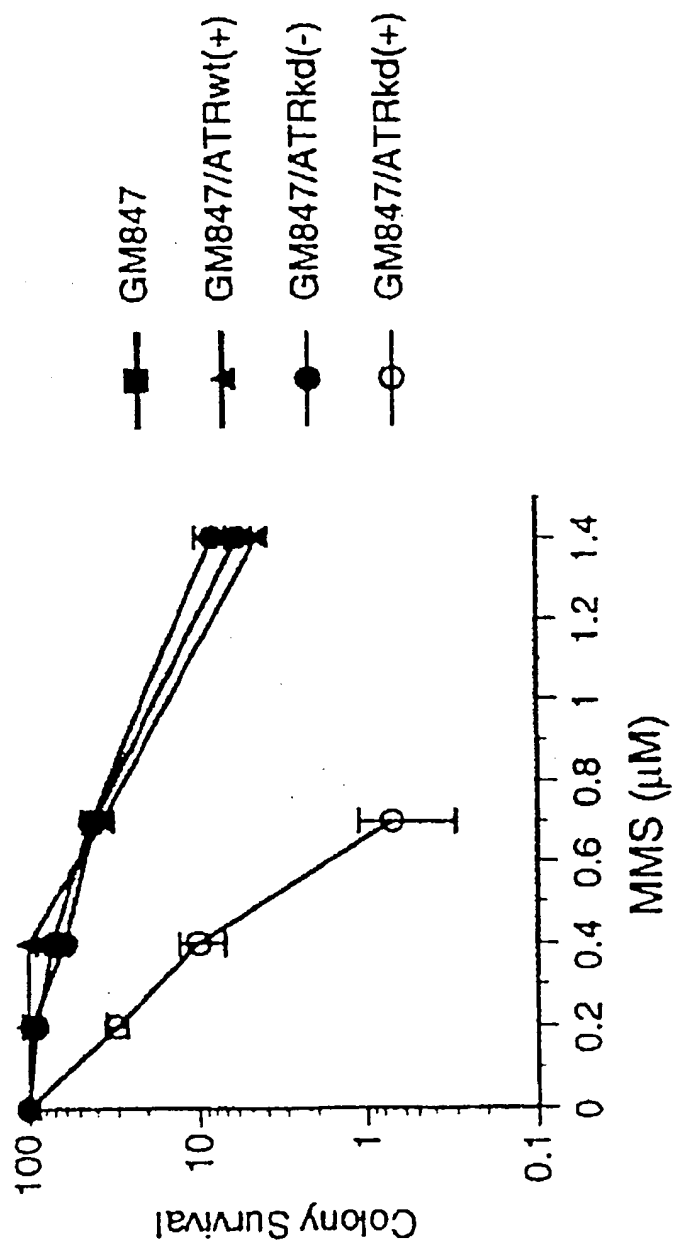


Figure 7